REMARKS

The courtesies extended by Examiner Rao during the telephone interview of March 14, 2007 with the undersigned are acknowledged with appreciation.

A. Status of the Claims

Claims 68, 138, 142, and 145-192 are pending.

B. Statement of Substance of Interview

During the interview of March 14, 2007, the rejections of the present claims were discussed in view of GB 953,997 ("the '997 reference") and U.S. Patent No. 4,375,477 to Bey et al. ("the Bey reference") as follows:

1. GB 953,997

In the Office Action of December 19, 2006, the Examiner stated that the '997 reference "teaches that β-alanine provides very effective protection against vasomotor or general cutaneous incidents." Applicants discussed that in the Office Action, the term "vasomotor" as used in the '997 reference appeared to be read out of context as being related to epilepsy and convulsive disorders.

During the interview, it was discussed that in the term "vasomotor or general cutaneous incidents", the word "vasomotor" is used to modify "cutaneous". Therefore, the term "vasomotor" is used in the '997 reference with respect to conditions of the skin and not with respect to epileptic conditions.

In support of this statement, the Examiner was directed to page 2, lines 106-110 of the GB reference which states as follows under the heading "Action against reactions of the allergic type":

"Recent experiments revealed in particular that in the case of a penicillic allergy β-alanine stopped in 30 minutes an alarming respiratory and vasomotor cutaneous process."
(Emphasis added)

The Examiner was further directed to page 2, line 121 to page 3, line 2, which states:

"To summarize, β-alanine provides a very effective protection in man against vasomotor or general cutaneous incidents which are usually attributed to an excess of histaminemia."
(Emphasis added)

In view of the sections of the '997 reference presented above, it was discussed that in the term "vasomotor or general cutaneous incidents" the term "vasomotor" is used to modify "cutaneous" and refers back to the term "vasomotor cutaneous" as used on page 2, line 109.

Applicants further discussed that the "vasomotor cutaneous" incidents discussed in the GB reference are of the allergic type due to an excess of histamenia (page 3, line 2 of the '997 reference), which is not related to epilepsy. It was discussed during the interview that vasomotor changes to the skin include, e.g., red, mottled or ashen color and temperature change.

During the interview, the Examiner indicated that he understood our position and requested that we present a written argument for his further consideration.

2. U.S. Patent No. 4,375,477

In the Office Action of December 19, 2006, the Examiner stated that with respect to the Bey reference, "the instant claims read on the therapeutic use of the reference disclosed compound."

During the interview, it was discussed that the compounds of the instant claims and the "compounds of the invention" described in the Bey reference do not overlap and are directed to distinct compounds. The Examiner was directed to the description of the Bey reference at column 2 lines 14-24 that the "compounds of the invention" have a mandatory substitution of a monofluoromethyl or difluoromethyl at the two carbon linking group of Formula I. Applicants discussed that the present claims do not encompass monofluoromethyl or difluoromethyl substitutions of the two carbon spacer unit of the present claims.

It was further discussed that a trifluoromethyl compound (Compound E) was tested by the Bey reference in Example 13. However, the Bey reference stated that "in the case of Compound E, there was no protection against the seizures; indeed the seizures appeared to be potentiated." (Emphasis added).

Accordingly, it was discussed that the testing of Compound E in Example 13 does not anticipate the methods of treating a convulsive disorder as recited in independent claims 138 and 142, as Example 13 reports that the trifluoromethyl compound is "inactive" at Table 1, column 18 of the Bey reference.

During the interview, the Examiner indicated that he understood our position and requested that we present a written argument for his further consideration.

II. REJECTION UNDER 35 U.S.C. § 102(b)

A. Rejection in view of GB 953,997.

In the Office Action, the Examiner rejected claims 68, 138, 142, and 145 on the grounds of being anticipated by GB 953,997 ('the '997 reference"). The Examiner stated that "the instant claims read on the therapeutic use of the reference disclosed compound. The reference teaches a β–alanine compound ... and the corresponding therapeutic use of the compound. The reference teaches that the compound showed activity on neurological accident, specifically in a case of epilepsy."

In view of the discussion presented during the interview and set forth above, the Examiner is requested to withdraw the present rejection.

Applicants further resubmit the previous arguments presented in the last response that the '997 reference does not teach or suggest that β–alanine has any effects on epileptogenesis. Rather, the '997 reference describes that β–alanine has the following actions:

1. Action against sudden flashes;
2. Protection against redness and congestive phenomena caused by nicotinic acid, and its salified or esterified derivatives; and
3. Action against reactions of the allergic type

(see page 2, lines 84-115 of the '997 reference).

Applicants respectfully submit that the example in the '997 reference which "showed activity on neurological accident, specifically in a case of epilepsy" was an admixture of β–alanine and lysine nicotinate. Applicants respectfully submit that in this example, the intent of the lysine nicotinate administration was to treat epilepsy and the intent of the β–alanine administration was to treat the side effects associated with the lysine nicotinate administration. This is evident at page 2, line 21 to page 3, line 12 of the '997 reference which states as follows:

> *"...β–alanine provides a very effective protection in man against vasomotor or general cutaneous incidents which are usually attributed to an excess of histaminemia ... produced in certain cases by the administration of nicotinic acid and pharmaceutically acceptable salified or esterified derivatives thereof and in particular lysine nicotinate, with which the β–alanine can thus be admixed so as to avoid their secondary effects..." (Emphasis added)*

In view of the description in the '997 reference, one skilled in the art would recognize that the β–alanine/lysine nicotinate admixture utilized the lysine nicotinate with the intent to treat epilepsy and utilized β–alanine with the intent to treat the side effects of the lysine nicotinate. Therefore, this reference does not anticipate the present claims. This position is supported by Rapoport v. Dement, 254 F.3d 1053, 1059 (Fed. Cir. 2001).

In Rapoport, the claim at issue stated in relevant part "[a] method for treatment of sleep apneas comprising of a therapeutically effective regimen ... [of buspirone] to a patient in need of such treatment ...." *254 F.3d at 1056.* Rapoport argued that prior art anticipated the claim. The Board of Patent Appeals and Interferences found that although the prior art addressed treatment of a symptom of sleep apnea, the prior art did not address treatment of sleep apnea. *Id. at 1060.* The Court affirmed, reasoning in part that "there is no disclosure in [the prior art] of tests in which buspirone is administered to patients suffering from sleep apnea with the intent to cure the underlying condition." *Id. at 1061.* (Emphasis added) The Court noted that the prior art mentioned the possibility of administering buspirone to patients with sleep apnea, but explained that it was "for the purpose of treating anxiety in such patients, not *for the purpose of* treating the sleep apnea disorder itself[.]" *Id.* (Emphasis added). Thus, the Court rejected Rapoport's argument that the reason for administering buspirone to the patient was irrelevant. *Id.*

In view of Rapoport, Applicants respectfully submit that as the β–alanine in the '997 reference was administered to an epileptic patient without an intent to treat the epilepsy, but rather to treat the side effects of lysine nicotinate, the reference does not anticipate the present claims.

Therefore, the Examiner is requested to remove the anticipation rejection of claims 68, 138, 142, and 145 over the '997 reference.

B. Rejection in view of U.S. Patent No. 4,375,477 to the Bey reference

In the Office Action, the Examiner rejected claims 68, 138, 142, and 145 on the grounds of being anticipated by the Bey reference. The Examiner stated that "the instant claims read on the therapeutic use of the reference disclosed compound. The reference teaches a substituted β–alanine compound, see the structural formula I in col. 2, and the corresponding therapeutic use of the compound. The reference teaches that the compound is useful in the treatment of central nervous system disorders such as seizure disorders associated with epilepsy, see col. 3, lines 38-43."

In view of the discussion presented during the interview and set forth above, the Examiner is requested to withdraw the present rejection.

Applicants respectfully submit that the Bey reference does not anticipate the method of claim 68 as the reference does not report any testing for the inhibition of epileptogenesis, which is the process whereby normal brain is transformed into a state suspectible to seizures (see page 1, lines 22-26 of the specification). In support of this position, Applicants direct the Examiner to the text of *Rational Polypharmacy*, Leppik, Ed. (ISBN:0-444-82455-3, Elsevier Science BV, 1996) by E. Lothman (pp. 3-7) and D. Lowenstein (pp. 45-60) which were submitted in the last response. Lothman defines *ictogenesis* as processes involved in initiation, elaboration and extension of seizures. Epileptogenesis, on the other hand, is a different phenomenon, and is defined as long-term, progressive changes in neural networks that eventually provoke spontaneous and recurring seizures. Epileptogenesis involves processes that take place before the first seizure occurs, rendering the epileptic brain susceptible to spontaneous recurrent seizures, which processes serve to intensify seizures and make them more refractory to therapy.

Applicants note that in addition to tests for anti-ictogenesis, the present application describes a test of anti-epileptogenesis at page 65, lines 3-31 of the specification as filed. Epileptogenesis is not described in the Bey reference and no test for anti-epileptogenesis is described in the Bey reference.

Applicants submit that anti-epileptogenic compounds as disclosed in the present invention are administered following a brain injury in order to prevent epileptogenesis. In the anti-epileptogenic test described in the specification as filed at page 65, lines 3-31, pilocarpine is injected in an animal to induce a prolonged seizure state, *status epilepticus*, that is used to produce a reproducible brain injury. Following the cessation of *status epilepticus* of Day 1, the test compound is administered at Time 1 (20 mg/kg/day i.v. for 10 days). In control studies, the animal is then observed, and starting on Day 13-15 the animal has spontaneous recurrent seizures. An effective anti-epileptogenic test

compound either reduces the number of spontaneous recurrent seizures or the animal does not go on to develop spontaneous recurrent seizures at all. Therefore, in the anti-epileptogenic test of the present invention, a test compound is administered after the initial brain injury (as simulated by the onset of *status epilepticus*), with no additional seizure-inducing stimuli, to monitor the occurrence of spontaneous recurrent seizures. This is different from the anti-ictogenic tests of the Bey reference wherein the test compound is given to the animal prior to the seizure-inducing stimulus.

The experimental models of the present application distinguish between the anti-ictogenic process and anti-epileptogenic processes as exemplified on page 65, lines 18-21, wherein compounds are administered at two separate time periods to assess the ability to suppress epileptogenesis and ictogenesis, respectively. As noted on page 65, lines 18-21, administration of the candidate compound at Time 1 (Day 1) (in the absence of any seizures) permits evaluation for anti-epileptogenic properties (ability to prevent the onset of seizures) and administration of compounds at Time 2 (day 30) permits evaluation of drugs as anti-ictogenic agents with the ability to suppress initiation, elaboration and extension of seizures.

Applying these definitions, Applicants respectfully submit that the Bey reference does not and cannot anticipate the method of inhibiting epileptogenesis as recited in claim 68. In column 19 of the Bey reference, it is stated that Compounds A-E were tested "to determine the extent of protection against mercapto propionic acid induced seizures." Clearly, this description in the Bey reference is directed to the use of the compounds therein to suppress ictogenesis and the compounds are not administered to inhibit epileptogenesis. Therefore, the Bey reference cannot anticipate a method of inhibiting epileptogenesis, since in the experiments the intent of the Bey reference is to inhibit ictogenesis and not to inhibit epileptogenesis.

In view of the arguments presented above, the Examiner is requested to remove the anticipation rejection of claims 68, 138, 142, and 145 over the Bey reference.

IV. NONSTATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

In the Office Action, the Examiner provisionally rejected claims 68, 138, 142 and 145-186 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 60-99 of copending Application No. 10/272,249.

In response, Applicants respectfully submit that upon indication that the present claims are otherwise allowable, the filing of terminal disclaimer to overcome the Examiner's nonstatutory obviousness–type double patenting rejection of copending Application No. 10/272,249 will be considered.

Further, the Examiner provisionally rejected claims 68, 138, 142, 145 and 151-162 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 60-99 of copending Application No. 11/099,232.

In response, Applicants note that copending Application No. 11/099,232 has been expressly abandoned by virtue of a concurrently filed paper, a copy of which is enclosed for the Examiner's convenience. Accordingly, Applicant respectfully requests that the double patenting rejection over copending Application No. 11/099,232 be removed.

V. CONCLUSION

Applicants respectfully submit that this application is now in condition for allowance.

An early and favorable action on the merits is earnestly solicited. The Examiner is invited to contact the undersigned at the telephone number provided below if he believes that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,

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